REMARKS

Claims 5, 9, and 12 - 16 were pending in the application. Claims 5, 9, and 12 – 16 have been amended. Claims 1- 4, 6 – 8, and 10 – 11 have been cancelled without prejudice. No new claims have been added. Support for the amendments to the claims can be found in the specification and claims as originally filed. No new matter has been added.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Claim Objections

The Examiner has objected to claims 5, 9, 12 – 16 because of minor informalities. The Examiner indicates that "claims 5, 9, 12 – 16 recite 'phospholipidosis non-inducing compounds' (and) it appears the claims wish the limitation to be drawn to compounds that do not induce phospholipidosis, however the recitation 'non-inducing appears to suggest the compounds have an effect in counteracting phopholipidosis induction, which based on the specification is not the intent." (Office Action, p.2).

Applicants have amended the claims to reflect that the compounds are either known to induce phospholipidosis or not to induce phospholipidosis. Accordingly, Applicants respectfully request that the foregoing objection be withdrawn.

The Examiner indicates that "claim 15 recites, 'wherein the average variation rate is the following formula…' (and) (t)hus claim 15 appears to be defining the average variation rate." (Office Action, p.2). The Examiner indicates that "(i)f the intent of the claims is to calculate the average variation rate by the formula, claim 15 should be amended to recite, 'wherein the average variation rate is calculated by the following formula.' (Office Action, p.2).

Applicants have amended claim 15 to provide further clarification and respectfully request that the objection be withdrawn.

The Examiner indicates that "claim 16 is objected to as it recites, 'the phospholipidosis is induced in an organ or tissue derived from the mammalian cell being exposed to the compound' (and) the claim appears to be asserting that a tissue or organ is derived from a mammalian cell, however cells are derived from tissue." (Office Action, p.3).

Applicants have amended claim 16 along the lines of the Examiner's suggestion and respectfully request that the objection be withdrawn.

Rejections Under 35 USC §112, Second Paragraph

The Examiner has rejected claims 5, 9, and 12 – 16 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree.

The instant claims recite a method for predicting a phospholipidosis induction potential of a test compound, which comprises determining a standard value for the judgment of the presence or absence of a phospholipidosis induction potential of the test compound (a) exposing samples containing mammalian cells to each of two or more compounds known to induce phospholipidosis and two or more compounds known not to induce phospholipidosis; (b) detecting expression variation of a set of genes set forth as SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23, in individual samples, (c) taking a fold change of the expresstion amount of each gene as an expression variation rate (X) of the gene when the expression amount increased upon exposure and taking an inverse number of fold change of the expresstion amount of each gene as an expression variation rate (X) of the gene when the expression amount decreased upon exposure, (d) calculating an average value of the expression variation rates of the 12 genes according to the following formula and determining as an average expression variation rate for each compound: [average expression variation rate] = m_1X_1+m2X2+ ... +$m_{12}X_{12}$ (m_1+m_2+ ... +m_{12}=1), wherein X_i (i=1-12) is the expression variation rate of each gene, m_i (i=1-12) is the weight of each gene and m_ix12=0.2-5; (e) determining, as the standard value, a cut-off value of average variation rate capable of

correctly judging the presence or absence of a phospholipidosis induction potential of the above-mentioned compounds known to induce or not to induce phospholipidosis with the probability of not less than about 70%; and predicting a phospholipidosis induction potential of the test compound, comprising (a) detecting expression variation of a set of genes set forth as SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23, in a sample containing the mammalian cell exposed to the test compound, (b) calculating an average value of the expression variation rates of the 12 genes according to the formula shown in the step (1)(c) and determining as the average expression variation rate for the test compound, (c) comparing the average expression variation rate for the test compound with the standard value obtained by the step (1); and (d) predicting that the test compound has a phopholipidosis induction potential when the average expression variation rate for the test compound is not less than the standard value.

The Examiner argues that "claims 5, 9, 12 – 16 are indefinite because it lacks a positive active step relating back to the preamble…(and) the claim does not present an actual step of predicting a phopholipidosis induction potential." (Office Action, p.3).

The claims have been amended to recite an active step relating back to the preamble by the phrase "predicting that the test compound has a phospholipidosis induction potential" in step 2(d) of claim 5.

The Examiner argues that the claims 'are indefinite as step 1(a) is drawn to detecting expression in samples containing a mammalian cell exposed to two or more known phopholipidosis-inducing compounds (and) it is unclear how treating a single cell with 4 different compounds with two different effects results in a standard." (Office Action, p.4).

Step 1(a) – (e) have been amended to clearly set forth the steps comprising determining a standard value for the judgement of the presence or absence of a phopholipidosis induction potential of the test compound.

The Examiner argues that "claims 5, 9, 12 – 16 are indefinite as they recite 'an average variation rate capable of correctly judging the presence or absence of the phopholipidosis induction potential of the above mentioned compounds by not less than about 70% based on the relationship between an average expression variation rate of the genes and the phopholipidosis induction potential…and (i)t is unclear in the claims presented what the metes and bounds of the relationship encompass." (Office Action,

p.4).

The claim have been amended to clearly indicate what is being varied by 70%, where step 1(e) recites determining, as the standard value, a cut-off value of average variation rate capable of correctly judging the presence or absence of a phopholipidosis induction potential of the above-mentioned compounds known to induce or not to induce phopholipidosis with the probability of not less than about 70%.

The Examiner argues that "claims 5, 9, 12 – 16 are indefinite as (1)(b) is drawn to using, as a standard value an average variation rate." (Office Action, p.5). The Examiner argues that "claim 5 recites the limitation 'the average variation rate of gene expression with the value obtained by step 1' in 2(b) (and) there is insufficient antecedent basis in step 2 for step 1." (Office Action, p.5).

Applicants have amended step 1 and step 2 to further clarify the method as claimed.

The Examiner argues that "claim 12 recited the limitation 'the mammal cell' in the second line (and) there is insufficient antecedent basis for this limitation in this claim." (Office Action, p.5).

Applicants have amended claim 12 as the Examiner has suggested.

The Examiner argues that "claims 12 and 13 recited the limitations 'the phopholipidosis inducing compound' or 'the phopholipidosis non-inducing compound' in the second line (and) there is insufficient antecedent basis for this limitation in the claim." (Office Action, p.5).

Applicants have amended the claims to recite proper antecedent basis.

The Examiner argues that "claim 16 recites the limitation 'the compound' in the last line (and) the metes and bounds of the claims are unclear as claim 5 from which it depends recites 'phopholipidosis inducing compounds,' 'non- phopholipidosis inducing compounds,' and 'test compounds' thus it is unclear to which compound this limitation is referring." (Office Action, p.6).

Applicants have amended claim 16 to further clarify that the phospholipidosis is induced in an organ or tissue from which the mammalian cell exposed to the test compound is derived.

Accordingly, in view of the above amendments, Applicants respectfully request that the foregoing rejections be withdrawn.

Rejections Under 35 USC §103(a)

The Examiner has rejected claims 5, 12, 13, 15 and 16 under 35 USC §103(a) as being unpatentable over Reasor et al. (Exp Biol Med (2001) volume 226, pages 825-830) in view of Mendrick (WO02/10453), Zhou Curr Opin Drug Discovery and Development (2003) volume 6, pages 339 – 345) as evidenced by Affymetrix blast searches printed 6/29/2009.

The Examiner has rejected claim 14 under 35 USC §103(a) as being unpatentable over Reasor et al. (Exp Biol Med (2001) volume 226, pages 825-830) in view of Mendrick (WO02/10453), Zhou Curr Opin Drug Discovery and Development (2003) volume 6, pages 339 – 345) as evidenced by Affymetrix blast searches printed 6/29/2009 and further in view of Jan-Peter (Exp Toxic Pathology (2004) volume 55, pages 347 – 355).

For the sake of brevity, the rejections under 103(a) are addressed together because each rejection relies on the Reasor et al., Zhou and Affymetrix references.

Applicants respectfully traverse the foregoing rejections.

Claim 5 has been set forth above. Claim 14 depends from claim 5 and recites that the compound known not to induce phospholipidosis is selected from the group consisting of acetaminophen, clarithromycin, disopyramide, erythromycin, flecainide, haloperidol, levofloxacin, ofloxacin, procainamide, quinidine, sotalol, sulfamethoxazole and sumatriptan.

No combination of references as cited by the Examiner teaches or suggests the claimed invention.

Nowhere does the Reasor reference teach or suggest a method for predicting a phopholipidosis induction potential of a test compound as claimed, where the method comprises determining a standard value for the judgment of the presence or absence of a phospholipidosis induction potential of the test compound, which comprises **detecting an average value of expression variation rate of a set of 12 genes set forth as SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23**, in individual samples.

None of the Zhou, Affymetrix or Jan-Peter references cure the flaws of the Reasor reference. None of Zhou, Affymetrix or Jan-Peter alone or in combination with

the Reasor reference teaches or suggests all the elements of the present claims.

In the method of the present invention, an average value of expression variation rate in **a set of genes set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23** is calculated by the formula shown in instant claim 5, and compared with a standard value determined by the criteria set forth in the claim. It would not have been obvious to a skilled artisan to choose **the set of 12 genes** as defined in the claim, and to use the average value of expression variation rate of the 12 genes as an index for predicting a phospholipidosis induction potential of a test compound.

The Examiner argues that "Reasor teaches that phopholipidosis is a recognized pre-clinical toxological problem in the pharmaceutical industry (and) that exposure to phospholipidosis inducing compounds results in the sequestration into lamellar bodies (and) the use of biomarkers to evaluate damage to cells would be helpful." (Office Action, p.7). The Examiner admits that "Reasor does not teach predicting phopholipidosis induction potential of a test compound by comparison to a standard value generated from other compounds known to have toxicological responses or known not to have toxicological responses (and) Reasor does not teach measuring the gene expression of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23."

None of the other cited documents disclose or suggest calculating an average value of expression variation rate of the 12 genes according to the method as Applicants disclose and claim.

The Examiner argues "the specification teaches that Mendrick discloses methods of predicting toxicity of a test compound, which comprises the examining of expression of between 2 to 100 genes selected from an enormous group of genes in the presence of a test compound and comparing the results with average expression amounts of respective genes previously calculated using known positive and negative compounds." (Office Action, p.8).

The Mendrick reference fails to remedy the defects of the Reasor reference.

The Mendrick reference discloses methods of predicting the toxicity of a test compound, which comprises examining the expression of 2 – 100 genes in the presence of a test compound and comparing the expression of individual genes with the average expression amounts of individual genes for known phopholipidosis-positive and

phopholipidosis-negative compounds. Nowhere does the Mendrick reference disclose or suggest calculating an average value of expression variation rate of the 12 genes according to the method as Applicants disclose and claim.

The Zhou reference does not cure the defects of the Reasor or Mendrick references.

The Examiner argues that "Zhou et al. teaches HU133A which comprises probes for the detection of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 (and) Affymetrix blast searches demonstrates that HU133A gene chip comprised SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23." (Office Action, p.9). However, nowhere does Zhou disclose or suggest calculating an average value of expression variation rate of the 12 genes according to the method as Applicants disclose and claim.

The Examiner reasons, "therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the microarray toxicological method of Mendrick to phopholipidosis involved in toxicity as taught by Reasor (and) the artisan would be motivated to apply the teachings of Mendrick to Reasor because Reasor suggests the use of biomarkers for phopholipidosis inducing compounds, while Mendrick demonstrates the use of nucleic acid expression as biomarkers (and) the HU-133A was already known…(and) probes to all the claimed SEQ ID NO were present on the HU-133 chip." (Office Action, p.9). Applicants disagree.

None of the cited references, taken alone or in combination, teach or suggest the present invention as claimed.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

Conclusion

In view of the above arguments and amendments, Applicants believe the pending application is in condition for allowance. If a phone call with the Applicant's attorney would help to expedite prosecution, the Examiner is urged to contact the undersigned.

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Respectfully submitted,

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